DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6006

July 25, 2002

CERTIFIED MAIL –
RETURN RECEIPT REQUESTED

Ben J. Lipps
Chief Executive Officer
Fresenius Medical Care
95 Hayden Avenue
Lexington, MA 02173

WARNING LETTER

02-NWJ-27

Dear Mr. Lipps:

During an inspection of your firm, Fresenius Medical Care, located at 1816 Underwood Blvd., Delran, N.J. between April 2, 2002 – May 3, 2002, investigators from the Food and Drug Administration (FDA) determined that you manufacture Naturalyte Acid Concentrate for bicarbonate hemodialysis. This product is a medical device within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

The above stated inspection revealed that your device is adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packaging, storage, or installation are not in conformance with the Quality System Regulation (QSR) for medical devices as set forth in Title 21, Code of Federal Regulations (CFR) Part 820. The deviations from QSR include, but are not limited to, the following:

1. Your Material Review Board, the Quality Assurance Unit, and Management failed to investigate and document the cause of the nonconformities relating to product, processes, and the quality system as required by 21 CFR 820.100 (a)(2) & (b). Your Quality System Policy Manual under section QSP-9 states that "the goal of all directed investigations is to establish the root cause of the failure." For example:

    A. Chemistry analysts recalibrated the equipment and repeated the analysis for out of specification results 69.785mEq/L (potassium) and 86.953mEEq/L (calcium) for Naturalyte Acid Concentrate lots 1ND069K3 (dated October 8, 2001) and 2CD973Ca1 (dated March 25, 2002), respectively, without a failure investigation. However, the controls for the equipment were within specifications according to your procedure 10.7

Rev. 8, "Analytical Control Methods for the AA Spectrophotometer"; therefore, recalibration was not appropriate. The specifications for Potassium for lot 1ND069K3 were [redacted] and for calcium for lot 2CD973Ca1 were [redacted]

B. There is no reference in your procedures that analysts have the option to recalibrate after out of specification results are determined, see 1.36 Rev 9, "Determination of Sodium, Potassium, Calcium and Magnesium in Naturalyte Concentrate and Dry Packs by Atomic Absorption Spectroscopy" and 10.7 Rev 8, "Analytical Control Methods for the AA Spectrophotometer". The instrument will automatically recalibrate [redacted] if the control sample is outside the percent recovery defined in your procedure 10.7 Rev 8.

The Out-Of-Specification (OOS) investigations dated May 13, 2002, provided in your May 16, 2002 response and generated after the FDA investigators' findings for lots 2CD973CA1 and 1ND069K3, are not adequate because they do not identify any assignable causes for the out of specification results. Your response dated July 16, 2002 states that you found an additional [redacted] out of specification (OOS) results that have not been investigated. We understand that you plan on performing a retrospective investigation for these [redacted] out of specification results. However, according to your response dated May 16, 2002, the investigations performed for lots 1ND069 and 2CD973 were performed retrospectively without verifying the root cause of the failures. Based on this response, we do not have a basis for concluding that the planned investigation for these sixteen OOS results will be adequate.

C. Unusual Incident Reports 2002D007 (dated January 14, 2002), 2002D010 (dated January 28, 2002), and 2002D020 (dated January 28, 2002) document environmental monitoring above the action limits established for TSA and SDA without determining the source of the microbe contamination. The microbes were detected in the drum fill room in the air, and on the packaging equipment surface for the Naturalyte Acid - Concentrate. These microbes were identified as Penicillium species, Cladosporium Cladosporioides, Mucor Plumbeus, Cryptococcus Neoformans, Hansenula Anomala, and Erwinia Rhapontici.

Your Material Review Board, the Quality Assurance Unit and Management must identify the actions needed to prevent recurrence of non-conforming product and other quality problems as required in 21 CFR 820.100(a)(3). A prerequisite to this identification processes is the documented investigation of the cause of the nonconformities relating to the product, processes, and quality system, as required by 21 CFR 820.100(a)(2) & (b). The inspection identified several instances in which this was not done. For example, although

Corrective Preventive Action Request (CPAR) 02002 was initiated to pursue ways to improve the environment, there is no indication that the root cause of the environmental concerns has been determined. Identification of the root cause of the issue is necessary in order to prevent reoccurrences of the microbes, and have an effective corrective and preventive action plan.

2. Your Material Review Board, the Quality Assurance Unit, and Management failed to evaluate the need for an investigation and notification of the persons or organizations responsible for the nonconformance, as required by 21 CFR 820.90(a). For example:

   A. Chemistry analysts observed out of specification results for lots 1ND069K3 (dated October 8, 2001) and 2CD973Ca1 (dated March 25, 2002) but did not evaluate whether a documented investigation was needed.

   The statement in your response dated May 16, 2002 that an OOS report was not appropriate because the "analyst should not knowingly continue an assay they expect to invalidate later for assignable cause," such as [redacted] is not adequate because your firm did not document any errors for the out of specification results for 2CD973CA1 and 1ND069K3. OOS investigations 2480 and 2481, generated after the FDA investigators' findings, documents that the drift for the AA Spectrophotometer was normal and the controls were within specifications according to your procedure 10.7 Rev. 8, "Analytical Control Methods for the AA Spectrophotometer".

   B. Your AAMI analysis report dated February 14, 2001 contained a copper result for process water collected on February 5, 2001 of 0.40 mg/L, which is above your specification of [redacted]. This out of specification result was not investigated until pointed out by the FDA investigators during this inspection. This process water is used for the manufacturing of Naturalyte Acid Concentrate.

3. Your Quality Assurance Unit and Management that have executive responsibility failed to ensure that an adequate quality system has been established and maintained as required by 21 CFR 820.20. For example:

   A. Although your management representatives issued corrective action requests from Unusual Incident Reports, your Management and Quality Assurance Unit with executive responsibility failed to ensure their timely correction and completion prior to the time of the inspection. For example, Corrective Preventative Action Request (CPAR) 01005, opened September 5, 2001 with a due date of October 30, 2001; CPAR 01006,

opened October 4, 2001 with a due date of February 15, 2002; and CPAR 01008, opened December 3, 2001 with a due date of January 31, 2002, were all still open as of the conclusion of the inspection on May 3, 2002.

B. Your Management and Quality Assurance Unit failed to conduct Out of Specification (OOS) investigations for lots 1ND069K3 (dated October 8, 2001) and 2CD973Ca1 (dated March 25, 2002), respectively, when the controls were within specifications according to your procedure 10.7 Rev. 8, "Analytical Control Methods for the AA Spectrophotometer", dated September 29, 1998.

4. Your firm failed to validate the new salt delivery system for process deviation 2002-005 dated February 1, 2002 for Naturalyte Acid Concentrate lot 2B0017 as required by 21 CFR 820.75. Furthermore, the new computer software included with the new salt delivery system is not validated for its intended use as required by 21 CFR 820.70(i). The validation of computers or automated data processing systems that are part of production or the quality system must be validated to the extent possible to adequately assure performance. In addition, your Quality System Policy Manual under section 7.3 states that "all operations including process, equipment, tests, designs, or software which can affect product quality require the need for appropriate validations activities."

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and on the Form FDA483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems within your establishment's quality system. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be system problems, you must promptly initiate permanent corrective and preventive actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

We have received the written responses from your firm dated May 16, 2002, June 18, 2002, and July 16, 2002. We acknowledge your firm's commitment to the Quality System Regulations. However, with respect to certain observations, your responses do not provide sufficient detail for us to evaluate whether the referenced corrective actions are adequate. As a result, in order to complete our review, we will need more documentation of your corrective actions, as described in the paragraphs following 1.B., and 2.A., above, and in the paragraphs below.

Regarding your response to FDA483 observation 29, your firm commits to revising the CPAR procedure; however, the response does not provide any documentation to indicate that the CPAR's referenced in observation 29 have been adequately investigated with an effective corrective action.

Your response to FDA483 observation 28 documents test results for copper on May 14, 2002 by [redacted]. Attachment 28C states that the analytical method is for Dialysis water, where the samples submitted for analysis on May 2, 2002 to [redacted] were water. We need further documentation to show that Naturalyte Acid Concentrate products manufactured before and after February 5, 2001 were tested for copper.

Your response to FDA483 observation 11 states that employee errors are occurring during analysis of Naturalyte Acid Concentrate product lots 2CD939 and 1JD800. One employee placed the sample probe in the wrong sample tube resulting in an out of specification result, and another employee entered an incorrect calculation factor. You are responsible to ensure that an adequate quality system is in place, which would include an evaluation of the employees performing quality control and manufacturing activities at your firm.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the FDA without further informal notice to you. These actions include, but are not limited to, seizure, injunction and/or civil penalties.

Please notify this office in writing within fifteen working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. Your response should be directed to the New Jersey District, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Robert J. Maffei, Compliance Officer.

Sincerely,

Diana Aradia-Tee
for

Douglas I. Ellsworth
District Director
New Jersey District

cc: Richard J. Hojnowski
Operations Manager
1816 Underwood Blvd.
Delran, NJ 08075